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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/819,669	03/17/1997	THIERRY BOON	LUD-5253.5-D	1995

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EXAMINER	
GAMBEL, PHILLIP	
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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/819,669	BOON ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 183-191

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 183-191

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

1. Upon reconsideration, New Grounds Of Rejection are set forth herein.

Claims 183-191 are pending

Claims 1-182 have been canceled.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 183-191 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the reasons of record.

The instant claims are drawn to:

"An isolated MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1X SSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells" and compositions thereof.

It appears that the claimed tumor rejection antigen precursor is drawn to the E antigen precursor gene which is set forth in SEQ ID NO: 7 or SEQ ID NO: 8 (see Example 20-26, pages 37-46 of the specification).

The instant specification discloses in Example 21 (page 40) that the tumor rejection antigen precursor E antigen is identified by either a 2.4 kb genomic segment of 1.8 kb mRNA segment and that gene extends over about 4.5 kb.

Here, the specification does not provide sufficient written description of MAGE tumor antigen precursors as broadly claims based upon the limited disclosure/recitation of a limited number of nucleic acids encoding a specific MAGE-1, MAGE-2 or MAGE-3. There is insufficient written description of the structural attributes that define or distinguish a MAGE tumor rejection antigen precursor, including MAGE-1 tumor rejection antigen precursors from one another or other molecules.

Further, it is noted that the structure (e.g. sequences) of MAGE molecules differ from one another and that such MAGE molecules are classified as separate molecules (e.g. MAGE-1, MAGE-2, MAGE-3). On the other hand, the nucleic acid of each MAGE species (e.g. MAGE-1, MAGE-2, MAGE-3) hybridizes to SEQ ID NO: 8 at the recited conditions (e.g. see Example 25 , pages 43-44 of the instant specification).

Given the polymorphism and homology of MAGE tumor rejection antigen precursors; there is insufficient written description of the alternative or allelic forms of MAGE tumor rejection antigen precursors encoded by nucleic acids which hybridize to SEQ ID NO: 8 under the written description provision of 35 USC 112, first paragraph.

Ding et al. (Biochem. Biophys. Res. Commun. 202: 549-555, 1994) discloses that homologous MAGE-1 can be polymorphic (see entire document, particularly page 551, paragraph 1).

As noted by Brasseur et al. (Int. J. Cancer 52: 839-841, 1992), "MAGE-1 belongs to a family of closely related genes. This makes it impossible to evaluate its expression by hybridization of Northern blots with large probes, because these probes cross-hybridize with other genes of the MAGE family. However, expression of MAGE-1 can be measured specifically by reverse transcription and polymerase chain reaction (PCR) using oligonucleotide primers corresponding to MAGE-1 sequences that display several differences with the corresponding sequences of the other MAGE genes."

For example, the high degree of homology shared among members of the MAGE gene family makes it difficult to distinguish one MAGE tumor rejection antigen precursor (e.g. MAGE-1) from the other MAGE gene family members. For example, nucleic acid molecules which hybridize to SEQ ID NO: 8 do not necessarily define any particular tumor antigen precursor.

In discussing the perspectives of specific immunotherapy with tumor antigens, including MAGE-1, co-inventor Boon acknowledges that: "While these are exciting prospects, it is difficult to predict whether therapeutic success will be achieved, even if a significant increase in anti-tumor CTL is obtained by immunization" (Int. J. Cancer 54: 177-180, 1993; see entire document, particularly, page 178, column 2, paragraph 2).

Applicant appears to rely upon that these melanoma-associated antigens are processed and then certain processed peptides may be recognized by cytotoxic T lymphocytes (e.g., see page 2 of the instant specification). However, even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al., APMIS 106: 665-679, 1998).

In discussing the structure and expression of MAGE family genes, De Plaen et al. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family ..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function." (see page 367, column 2, paragraph 2).

It is noted that the MAGE genes do not seem to be expressed in normal tissues except testis and placenta (see De Plaen et al., page 368, column 1, paragraph 2). While the MAGE genes may have the potential to code for antigens that could be targets for specific anti-tumor T lymphocyte responses, such responses would rely upon various regions of the different MAGE proteins contributing peptides that combine with various HLA class I molecules (page 368, column 1, paragraph 2).

Therefore, the reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the processing and presentation of MAGE-derived peptides in an attempt to obtain cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB J 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells" (see page 2251, column 1, paragraph 1 of Tumor Antigens). "Attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty" (page 2251, column 2, paragraph 2).

Boon et al. (Cancer Cells 1: 25-28, 1989) discloses that "On the basis of these results, we now have a plausible explanation for the stability, frequency, and diversity of tum- variants. They are stable because they arise as a result of point mutations. They are extremely frequent and diverse, because mutations occurring throughout the whole genome can lead to the production of new antigenic peptides binding to class I MHC molecules so as to be recognized by the T lymphocytes of the host. They do not stimulate the production of antibodies because B cells may not be adapted to the recognition of a very low density of antigenic peptides bound to class I molecules" (see page 26, column 2, paragraph 2). "Are the TSTA like tum- antigens, the result of mutations occurring throughout the genome? Certainly, the large diversity of TSTA would be consistent with this notion" (see page 26, column 2, paragraph 3). "It would also imply that the TSTA bear no functional relation with the cellular modifications that lead to malignant transformation" (see page 27, column 1). "Only the cloning of the relevant genes and comparison of their sequences with those found in normal cells can give a complete answer to the problem. Thus, for man, the genetic approach probably will be required not only to establish the nature of TSTA but also to demonstrate their existence" (page 28, column 1).

Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen at the time the invention was made and recognized the requirement to demonstrate its existence.

In addition to defining human tumor antigens, the skilled artisan recognized the difficulties in defining a MAGE tumor rejection antigen precursor, given the homology and diversity of MAGE molecules and given the lack of correlation with between a particular structure(s) of a MAGE tumor rejection antigen precursor and its ability to increase an anti-tumor cytotoxic T lymphocyte response, particularly in vivo.

The instant application does not provide sufficient guidance as to the nexus or correlation between the structure and function of a MAGE tumor rejection antigen encoded by the claimed nucleic acid molecules that places the skilled artisan in possession of the relevant identifying characteristics of a genus of MAGE tumor rejection antigen precursors encoded by the myriad of nucleic acid molecules, commensurate in scope with the claimed invention.

Therefore, only the SEQ ID NOS: 7 and 8 provide for the amino acid and nucleic acid sequences of MAGE-1 tumor rejection antigen precursor meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Here, the specification does not provide sufficient written description of a tumor antigen precursor based upon the limited disclosure/recitation of a one nucleic acid encoding each different MAGE tumor antigen precursor. There is insufficient written description of the structure / sequences of nucleic acids or complementary sequences of which hybridize to SEQ ID NO: 8 and encode a MAGE tumor antigen precursor and, in turn, provide the appropriate structural and functional attributes of a MAGE tumor antigen precursor.

Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of MAGE tumor rejection antigen precursors encodied by the myriad of claimed nucleic acid molecules commensurate in scope with the claimed invention; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

4. Claims 183-191 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a MAGE-1 tumor antigen precursor encoded by SEQ ID NO: 8; does not reasonably provide enablement for any "an isolated MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1X SSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. nucleic acid or amino acid sequences) that distinctly identifies the breadth of MAGE tumor rejection antigens encoded by nucleic acids encoding tumor rejection antigen precursors which hybridize to SEQ ID NO: 8, encompassed by the claimed invention.

Applicant should limit the claims either to SEQ ID NO: 7 / SEQ ID NO: 8 that read on MAGE-1 as the elected invention (see applicant's election filed 12/9/97).

While the recitation of "tumor antigen precursor" may have some notion of the properties of the claimed molecule(s), claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use the "tumor antigen precursors", commensurate in scope with the claimed invention.

Ding et al. (Biochem. Biophys. Res. Commun. 202: 549-555, 1994) discloses that homologous MAGE-1 can be polymorphic (see entire document, particularly page 551, paragraph 1).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (Trends in Biotech. 18:34-39, 2000) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36).

Similarly, Bork (Genome Research 10:398-400, 2000) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399).

Smith et al. (Nature Biotechnology 15:1222-1223, 1997) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene

There is insufficient guidance and direction as to how to make and use the breadth of MAGE tumor rejection antigen precursors encoded by nucleic acids that hybridize to SEQ ID NO: 8; other than MAGE-1 encoded by SEQ D NO: 8 in the absence of structural or functional attributes that define a MAGE tumor rejection antigen precursor.

Tumor antigen precursors are processed to form the presentation of tumor rejection antigens (page 6 of the specification), including but not limited to those most characteristic of a particular tumor (page 8 of the specification)

A person of skill in the art is not enabled to make and use the breadth of MAGE tumor rejection antigen precursors, which can be processed to form the presentation of tumor rejection antigens and be characteristic of a particular tumor, commensurate in scope with the claimed invention. The skilled artisan would not have predicted that all that is required for a tumor antigen precursor is that it can be encoded by a nucleic acid of which hybridizes to SEQ ID NO: 8 . A skilled artisan would have expected that other structural and functional attributes would be required to provide for a nucleic acid to encode a MAGE tumor rejection antigen precursor and its ability to be processed to form a tumor rejection antigen characteristic of a particular tumor.

It appears that the claimed tumor antigen precursor is drawn to the E antigen precursor gene which is set forth in SEQ ID NO: 7 or SEQ ID NO: 8 (see Examples 20-26 of the specification).

The instant specification discloses in Example 21 that the tumor antigen precursor E antigen is identified by either a 2.4 kb genomic segment of 1.8 kb mRNA segment and that gene extends over about 4.5 kb as shown in Figure 8.

Here, the specification does not enable the breadth of MAGE tumor rejection antigen precursors encoded by the myriad of nucleic acid molecules that hybridize to SEQ ID NO: 8 as broadly claimed based upon the limited disclosure/recitation that SEQ ID NO: 8 encodes MAGE-1. There is insufficient guidance and direction as to the structural attributes that define or distinguish MAGE tumor rejection antigen precursors.

Further, it is noted that the evidence of record as well as applicant's comments in the current amendment note that the structure (e.g. sequences) of MAGE molecules differ from one another and that such MAGE molecules are classified as separate molecules (e.g. MAGE-1, MAGE-2, MAGE-3, MAGE-4, MAGE-5, MAGE-6, MAGE-7). Yet, the nucleic acid of each MAGE species (e.g. MAGE-1, MAGE-2, MAGE-3, MAGE-4, MAGE-5, MAGE-6, MAGE-7) hybridizes to SEQ ID NO: 8 at the recited conditions (see page 3, last paragraph of applicant's amendment, filed 12/19/02).

This is consistent with the instant application as filed wherein the specification discloses in Example 23 (page 19) that MAGE refers to a family of tumor rejection antigen precursors molecules which share a certain degree of homology. Example 25 (page 43) acknowledges that genes encoding MAGE-1, -2, -3 cross hybridized to a considerable extent.

Given the polymorphism and homology of MAGE tumor rejection antigen precursors; there is insufficient enablement of the alternative or allelic forms of MAGE tumor rejection antigen precursors, including MAGE-1 tumor rejection antigen precursors encoded by nucleic acids which hybridize to SEQ ID NO: 8 commensurate in scope with the claimed invention.

Ding et al. (Biochem. Biophys. Res. Commun. 202: 549-555, 1994) discloses that homologous MAGE-1 can be polymorphic (see entire document, particularly page 551, paragraph 1).

As noted by Brasseur et al. (Int. J. Cancer 52: 839-841, 1992), "MAGE-1 belongs to a family of closely related genes. This makes it impossible to evaluate its expression by hybridization of Northern blots with large probes, because these probes cross-hybridize with other genes of the MAGE family. However, expression of MAGE-1 can be measured specifically by reverse transcription and polymerase chain reaction (PCR) using oligonucleotide primers corresponding to MAGE-1 sequences that display several differences with the corresponding sequences of the other MAGE genes."

In discussing the perspectives of specific immunotherapy with tumor antigens, including MAGE-1, co-inventor Boon acknowledges that: "While these are exciting prospects, it is difficult to predict whether therapeutic success will be achieved, even if a significant increase in anti-tumor CTL is obtained by immunization" (Int. J. Cancer 54: 177-180, 1993; see entire document, particularly, page 178, column 2, paragraph 2).

Applicant appears to rely upon that these melanoma-associated antigens are recognized by cytotoxic T lymphocytes. This recognition by cytotoxic T lymphocytes relies upon the processing to form the presentation of tumor rejection antigens (see page 2 of the instant specification). However, even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al. (APMIS 106: 665-679, 1998).

In discussing the structure and expression of MAGE family genes, De Plaen et al. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family ..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function." (see page 367, column 2, paragraph 2).

Therefore, the high degree of homology shared among members of the MAGE gene family makes it difficult to distinguish one MAGE molecule (e.g. MAGE-1) from the other MAGE gene family members.

It is noted that the MAGE genes do not seem to be expressed in normal tissues except testis and placenta (see De Plaen et al., page 368, column 1, paragraph 2). While the MAGE genes may have the potential to code for antigens that could be targets for specific anti-tumor T lymphocyte responses, such responses would rely upon various regions of the different MAGE proteins contributing peptides that combine with various HLA class I molecules (page 368, column1, paragraph 2).

Therefore, the reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the processing and presentation of MAGE-derived peptides in an attempt to obtain cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMiS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB J 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells" (see page 2251, column 1, paragraph 1 of Tumor Antigens). "Attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty" (page 2251, column 2, paragraph 2).

Boon et al. (Cancer Cells 1: 25-28, 1989) discloses that "On the basis of these results, we now have a plausible explanation for the stability, frequency, and diversity of tum- variants. They are stable because they arise as a result of point mutations. They are extremely frequent and diverse, because mutations occurring throughout the whole genome can lead to the production of new antigenic peptides binding to class I MHC molecules so as to be recognized by the T lymphocytes of the host. They do not stimulate the production of antibodies because B cells may not be adapted to the recognition of a very low density of antigenic peptides bound to class I molecules" (see page 26, column 2, paragraph 2). "Are the TSTA like tum- antigens, the result of mutations occurring throughout the genome? Certainly, the large diversity of TSTA would be consistent with this notion" (see page 26, column 2, paragraph 3). "It would also imply that the TSTA bear no functional relation with the cellular modifications that lead to malignant transformation" (see page 27, column 1). "Only the cloning of the relevant genes and comparison of their sequences with those found in normal cells can give a complete answer to the problem. Thus, for man, the genetic approach probably will be required not only to establish the nature of TSTA but also to demonstrate their existence" (page 28, column 1).

Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen at the time the invention was made and recognized the requirement to demonstrate its existence.

In addition to defining human tumor antigens, the skilled artisan recognized the difficulties in defining a MAGE tumor rejection antigen precursors (e.g. MAGE-1), given the homology and diversity among MAGE molecules and given the lack of correlation with between a particular structure(s) between a MAGE tumor rejection antigen precursor and its ability to increase an anti-tumor cytotoxic T lymphocyte response, particularly in vivo.

The instant application does not provide sufficient guidance as to the nexus or correlation between the structure and function of MAGE tumor rejection antigen precursors that enables the skilled artisan to predict the relevant identifying characteristics of a genus of MAGE tumor rejection antigen precursors which hybridize to SEQ ID NO: 8.

A person of skill in the art could not predict which particular nucleic acids (or amino acid sequences) other than that was set forth in SEQ ID NO: 8 would be sufficient to confer the ability to encode a MAGE tumor antigen precursor and, in turn, wherein the MAGE tumor antigen precursor can be processed to form a tumor rejection antigen characteristic of a particular tumor

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using tumor antigen precursors encoded by nucleic acids of which the complementary sequence hybridizes to SEQ ID NO: 8, wherein the appropriate structural and functional features of a MAGE tumor antigen precursor (e.g. MAGE-1) would be maintained would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

5. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 183-191 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned U.S. Patent No. 6,025,474 in view of applicant's acknowledgement that the nucleic acid of each MAGE species (e.g. MAGE-1, MAGE-2, MAGE-3) hybridizes to SEQ ID NO: 8 at the recited conditions (see Example 25, pages 43-44 of the instant specification). Claims 1-2 of U.S. Patent No. anticipate instant claims 183-191.

7. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned , discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Commonly assigned U.S. Patent No. 6,025,474, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

8. Given applicant's acknowledgement that the nucleic acid of each MAGE species (e.g. MAGE-1, MAGE-2, MAGE-3) hybridizes to SEQ ID NO: 8 at the recited conditions (see Example 25, pages 43-44 of the instant specification), applicant should indicate commonly assigned USSNs or U.S. patents that read or anticipate the instant claimed recitation:

"An isolated MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1X SSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells" and compositions thereof.

9. No claim allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
February 25, 2004